UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Zinc Omadine:** Review of a Dermal Sensitization Study in Guinea Pigs.

EPA ID# 088002-001258
Case No. 819310

DP Barcode D225354
PC Code No. 088001

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I
Health Effects Division (7509C)

John Whalan
8-20-96

TO: Bruce Sidwell (PM Team # 53)
Special Review and Reregistration Division (7508W)

THRU: Roger L. Gardner, Section Head
Section 1, Toxicology Branch I
Health Effects Division (7509C)

Roger Gardner
8/21/96

KB
8/26/96

I. Background:

Inadequacy of the Existing Dermal Sensitization Study

Olin Corporation wishes to replace two inadequate dermal sensitization studies (MRID No. 42146705—DP Barcode D172957 and MRID No. 43372001—DP Barcode D208111) with a better one:

81-6 Delayed Contact Dermal Sensitization Test (Buehler Method).
Study No. MB 96-4868.06; February 28, 1996; MRID No. 43950201

II. Recommendations:

There was no evidence of dermal sensitization or irritation in any guinea pigs challenged with undiluted Zinc Omadine 48% Dispersion. This study, which was classified as **Acceptable** and satisfies data requirement 81-6 for a Dermal Sensitization study, replaces the previous equivocal studies. Zinc omadine is not a dermal sensitizer. The Data Evaluation Record and an updated Toxicology Profile are attached.

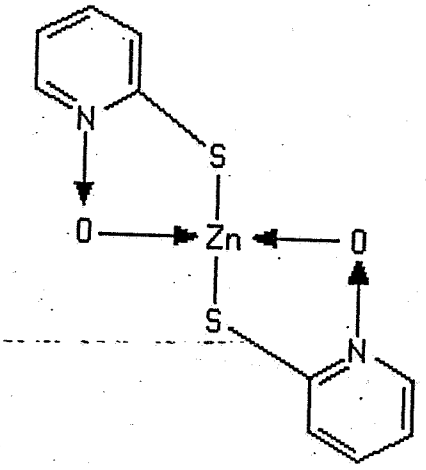
III. Data Requirements (CFR §158.35):

PC CODE: 088002

CASE NO.: 819310

CAS NO.: 13463-41-7

REGISTRANT: Olin Chemicals



REGISTERED USE PATTERNS: Siding, metalworking fluids, PVC plastics, PVC plastics (non-food contact surfaces), PVC tarpaulins, vinyl, shower curtains, synthetic polymers, vinyl wall coverings, vinyl coated fabrics, vinyl swimming pool liners, awnings, and tents.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Technical: **Zinc Omadine Powder** (Zinc Omadine Powder Industrial Microbiostat, Zinc Omadine Powder E85656 TER; 95% zinc pyrithione)
Zinc 2-pyridinethiol-1-oxide
Registration No. 1258-840
And
Zinc Omadine 48% Dispersion; (Zinc Omadine 48% Aqueous Dispersion Industrial Microbiostat; Zinc Omadine FPS - 48% a.i.)
Registration No. 1258-841

NOTE: Zinc Omadine 48% Dispersion was used in place of Zinc Omadine Powder in some studies. TB-I considers the 48% dispersion to be toxicologically equivalent to an aqueous dilution of the 95% powder. Two additives found in the dispersion, [redacted] and [redacted] are both innocuous (§180.1001).

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal sensitization
81-7	N	--	Acute Delayed Neurotoxicity (hen)

	Required	Satisfied	
82-1a	H,M*	N	Subchronic Oral (rodent)
82-1b	N	--	Subchronic Oral (nonrodent)
82-2	H*	N	21-Day Dermal
82-3	M,L*	Y	90-Day Dermal
82-4	M,L*	Y	90-Day Inhalation
82-7	N	--	90-Day Neurotoxicity Screening Battery (mammal)
83-1a	H*	N	Chronic Toxicity (rodent)
83-1b	H*	N	Chronic Toxicity (nonrodent)
83-2	H*	N	Carcinogenicity (two species)
83-3a	H,M,L*	Y	Developmental Toxicity (first species)
83-3b	H*	Y	Developmental Toxicity (second species)
83-4	H*	N	Reproduction
83-5	N	--	Chronic/Carcinogenicity (see 83-1 & 83-2)
84-2a	H,M,L*	Y	Mutagenicity - Gene Mutation
84-2b	H,M,L*	Y	Mutagenicity - Structural Chrom. Aberr.
84-2c	H,M,L*	Y	Mutagenicity - Other Genotoxic Effects
85-1	H*	Y	General Metabolism
85-2	N	--	Dermal Penetration
86-1	N	--	Domestic Animal Safety

Formulation: **Zinc Omadine 48% Dispersion** (Zinc Omadine 48% Aqueous Dispersion Industrial Microbiostat; Zinc Omadine FPS - 48% a.i.) Registration No. 1258-841 - See **Technical**

Y - Yes
N - No
W - Waived
P - Partially

* **H, M, L** - Required studies for High (**H**), Medium (**M**) and Low (**L**) Exposure Category uses, based on Bill Burnam's Memorandum, *Data Call-In Notices for Antimicrobials* (March 31, 1987).

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IV. Toxicology Profile:

Technical: **Zinc Omadine Powder** (Zinc Omadine Powder Industrial Microbiostat, Zinc Omadine Powder E85656 TER - 95% a.i.)
Registration No. 1258-840
And
Zinc Omadine 48% Dispersion (Zinc Omadine 48% Dispersion Industrial Microbiostat; Zinc Omadine FPS - 48% a.i.)
Registration No. 1258-841

NOTE: Zinc Omadine 48% Dispersion was used in place of Zinc Omadine Powder in some studies. TB-I considers the 48% dispersion to be toxicologically equivalent to an aqueous dilution of the 95% powder. Two additives found in the dispersion, [redacted] and [redacted] are both innocuous (§180.1001).

INERT INGREDIENT INFORMATION IS NOT INCLUDED

	STUDY	RESULTS
81-1	**Acute Oral (Gavage), Rat** [Zinc Omadine® 48% Dispersion] Acceptable Toxicity Category III (♂), II (♀) HED Document No. *?* Study MB 85-8049 A; 2-24-86 MRID No. 42827901	LD_{50} (95% c.i.): 630 mg/kg (438-906) in males 460 mg/kg (352-601) in females 560 mg/kg (427-734) in the combined sexes. **Clinical signs:** Ptosis, diarrhea, lethargy, piloerection, chromodacryorrhea, chromorhinorrhea, emaciation, soiling of body surfaces, and anogenital wetness and brown staining, alopecia, ataxia, bloated abdomen, and ocular abnormalities. **Gross pathology:** Abnormalities of the lungs, liver, spleen, and G.I. tract in dead rats; and abnormal spleens and peritoneal cavity adhesions in survivors. **Levels tested:** 260, 329, 417, 529, and 668 mg/kg in Wistar strain by gavage.
81-2	**Acute Dermal, Rabbit** [Zinc Omadine Powder] Acceptable / Toxicity Category III HED Document No. 10356 Study MB 91-707 B; 11-25-91 MRID No. 42146701	1 of 5 males died on day 2 without agonal signs. There were no female deaths. **Clinical signs:** Reduced hind limb mobility, diarrhea, reduced feces, and weight loss in females only. **Dermal scores:** Very slight erythema was found on day one in males (3/5), and in females (1/5). One male had very slight edema on day one. **Gross pathology:** Yellow-stained nose and mouth, congested lungs, pale intestines, and a yellow-stained dosing site in the male which died; and brown-stained anogenital area in the female with diarrhea. **Level tested:** Limit test of 2000 mg/kg dermally (aqueous paste) in New Zealand White strain.

	STUDY	RESULTS
81-3	**Acute Inhalation, Rat** [Zinc Omadine Powder] Acceptable / Toxicity Category III HED Document No. 10357 Study 397-051; 10-25-91 MRID No. 42146703	4-hour, nose-only LC_{50} >0.61 mg/L (probit analysis could not be done because only 2 concentrations were used - 0.24 and 0.61 mg/L); MMAD (gsd) - 1.9 - 2.3 μm (2.08 - 2.11) **Clinical signs:** Decreased activity, tremors, increased salivation, labored breathing, gasping, staining around the mouth, inhibited mean body weight gain in the high-concentration females, and death. **Gross pathology:** Multilobar lung congestion in the high-concentration group. **Levels tested:** 0.24 and 0.61 mg/L (analytical conc.), 4 hours, nose-only, MMAD (gsd) of 1.9-2.3 μm (2.08-2.11) in Sprague-Dawley CD® strain.
81-4	**Primary Eye Irritation, Rabbit** [Zinc Omadine Powder] Acceptable / Toxicity Category I HED Document No. 10358 Study MB 91-707 D R/A; 1-2-91 MRID Nos. 421546-01, 421467-02	Severe irritation was found in both washed and unwashed eyes as evidenced by corneal opacity, sluggish and unresponsive irises, beefy red conjunctivae, severe chemosis, and marked eye discharge. The unwashed eyes had no evidence of reversibility by day 7, so the rabbits were sacrificed for humane reasons. Pannus was found in all the washed eyes beginning on day 7. Only one of three washed eyes showed signs of reversibility by day 14. It appears that the test article is not easily washed out of the eye, and even in a well washed eye, there is great potential for severe eye trauma. **Level tested:** 0.1 ml in conjunctival sac of New Zealand White strain.
81-5	**Primary Dermal Irritation, Rabbit** [Zinc Omadine Powder] Acceptable / Toxicity Category IV HED Document No. 10359 Study MB 91-707 C; 11-25-91 MRID No. 42146704	Zinc omadine powder E85656 TER, moistened with distilled water, induced very slight erythema and slight edema which reversed after 48 hours. Only half the treated rabbits were affected, and there were no other clinical signs. **Level tested:** 0.5 g aliquots applied as an aqueous paste, occluded for 4 hours in Zealand White strain.
81-6	**Dermal Sensitization, Guinea Pig** [Zinc Omadine® 48% Dispersion] Acceptable HED Document No. *?* Study MB 96-4868.06; 2-28-96 MRID No. 43950201	There was no evidence of dermal sensitization or irritation in any guinea pigs. **Level tested:** 0.4 ml induction and challenge doses of undiluted Zinc Omadine 48% Dispersion in Hartley Albino strain. [Buehler Method]

	STUDY	RESULTS
82-1a	**3-Month Feeding, Rat** [Zinc Omadine Powder] Supplementary HED Document No. 3933 7-20-56	**Required for High and Medium Exposure Category uses only.** NOEL = 15 ppm LEL = 75 ppm (increased organ body weights for liver, kidney, and testes; decreased survival, hind limb weakness).
82-2	**21-Day Dermal**	**Data gap for High Exposure Category uses only.**
82-3	**90-Day Dermal - Rat** [Zinc Omadine 48% Dispersion] Acceptable HED Document No. *?* Study 397-057; 4-29-93 MRID No. 42827902	**Required for Medium and Low-Exposure Category uses only.** NOEL = 100 mg/kg/day in females; 1000 mg/kg/day in males. LOEL = 1000 mg/kg/day in females (decreased body weight gain, food consumption, and food efficiency); undefined in males; highest attainable dose. **Levels tested:** 0, 20, 100, and 1000 mg/kg/day, 6 hours/day, 5 days/week,13 weeks in CrlCD BR strain by dermal occlusion.
82-4	**90-Day Inhalation - Rat** [Zinc Omadine 48% Dispersion] Acceptable HED Document No. *?* Study 397-052; 5-17-93 MRID No. 42827903	**Required for Medium and Low-Exposure Category uses only.** Whole-body exposure; MMAD = 1.2-1.5μm NOAEL = 0.0005 mg/L/day LOEL = 0.0025 mg/L/day (labored breathing, rales, increased salivation, decreased activity, dry red-brown material around the nose, increased absolute and relative lung weights, death of undetermined cause). **Levels tested:** 0.0005, 0.0025, or 0.01 mg/L/day (analytical conc.), whole-body exposure, 6 hours/day, 5 days/week, 13 weeks in Sprague-Dawley strain.
83-1a	**Chronic Feeding, Rodent**	**Data gap for High Exposure Category uses only.**
83-1b	**Chronic Feeding, Nonrodent**	**Data gap for High Exposure Category uses only.**
83-2	**Carcinogenicity, Two species**	**Data gap for High Exposure Category uses only.**

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	STUDY	RESULTS
83-3a	**Developmental Toxicity, Rat** [Zinc Omadine 48% Dispersion] Acceptable HED Document No. *?* Study 397-055; 5-27-93 MRID No. 42827904	Maternal toxicity NOEL = 0.75 mg/kg/day Maternal toxicity LOEL = 3.0 mg/kg/day (excessive salivation during the dosing period). Developmental toxicity NOEL = 0.75 mg/kg/day Developmental toxicity LOEL = 3.0 mg/kg/day (increased incidences of fused ribs). **Levels tested:** 0, 0.75, 3, and 15 mg/kg/day by gavage on gestatation days 6-15 in Sprague-Dawley dams.
83-3b	**Developmental Toxicity, Rabbit** [Zinc Omadine 48% Dispersion] Acceptable HED Document No. *?* Study 397-056; 5-18-93 MRID No. 42827905	**Required for High-Exposure Category uses only.** Maternal/Developmental NOEL = 0.5 mg/kg/day. Maternal/Developmental LEL = 1.5 mg/kg/day (increased postimplantation loss and decreased number of viable fetuses; it is not clear whether the resorptions were due to maternal or developmental toxicity). **Levels tested:** 0, 0.5, 1.5, and 3.0 mg/kg/day by gavage on gestation days 6 - 18 in New Zealand White does.
83-4	**Reproduction**	**Data gap for High Exposure Category uses only.**
84-2a	**Gene Mutation:**	
	Ames Assay [Zinc Omadine 48% Dispersion] Acceptable HED Document Nos. 10288, 11549 Study T9153.501014; 10-19-90 MRID No. 41906502	Not mutagenic to *Salmonella* strains exposed up to cytotoxic doses with and without metabolic activation.
84-2b	**Structural Chromosome Aberration:**	
	CHO/HGPRT Mutation Assay [Zinc Omadine 48% Dispersion] Acceptable HED Document Nos. 10288, 11549 Study T9153.332001; 9-6-90 MRID No. 41906503	Negative for induction of gene mutation at the HGPRT locus of CHO cells exposed to cytotoxic doses with and without metabolic activation.

	STUDY	RESULTS
84-2c	**Other Genotoxic Effects:**	
	Micronucleus Assay in Mice [Zinc Omadine 48% Dispersion] Acceptable HED Document Nos. 10288, 11549 Study T9153.122; 10-22-90 MRID No. 41906501	Not clastogenic in bone marrow cells of mice treated I.P. up to toxic doses (44 mg/kg).
85-1	**Metabolism, Pig** [Zinc Omadine Powder] Minimum Study 36:523; 1976 HED Document No. 3933	**Required for High-Exposure Category uses only.** Significant bioretention and accumulation in renal hepatic and pancreatic tissues.

Formulations: **Zinc Omadine 48% Dispersion** (Zinc Omadine 48% Aqueous Dispersion Industrial Microbiostat; Zinc Omadine FPS - 48% zinc pyrithione) Registration No. 1258-841 - See **Technical**

TB-I has no toxicology data for the following registered formulations:

1. **Zinc Omadine PVC Industrial Fungicide** (5% a.i.; Registration No. 1258-1183)
2. **Omacide P-10 D Industrial Fungicide** (5% a.i.; Registration No. 1258-1184)
3. **Supercide** (3% a.i.; Registration No. 53707-1)

V. Data Gaps: Since all **High Exposure Category** uses in metal-working fluids are regulated by OSHA, there is no need to address the High Exposure data gaps unless new use patterns are requested. All other registered uses are in the **Low-Exposure Category**, and these data requirements have been satisfied.

VI. Action Taken to Obtain Additional Information or Clarification:

Deficiencies were identified by the Registrant and HED during FIFRA 88 review.

VII. Endpoints for Occupational Risk Assessment:

Reference Dose (RfD) - An RfD has not yet been defined.

Short Term Occupational or Residential Exposure (1 to 7 Days): To be determined when the data are presented to the Toxic Endpoint Selection (TES) Committee.

Intermediate Term Occupational or Residential (1 Week to Several Months): To be determined when the data are presented to the Toxic Endpoint Selection (TES) Committee.

Cancer Classification: Undefined. Carcinogenicity studies are not required for Low-Exposure Category use patterns.

VIII. Pending Regulatory Actions: There are at this writing no pending regulatory actions against the Registration of this pesticide.

IX. Toxicologic Issues Pertinent to Granting this Request: N/A

Compiled by John E. Whalan (Revised August 20, 1996)

[ZINC OMADINE] Dermal Sensitization – Guinea Pig (81-6)

EPA Reviewer: John E. Whalan
Review Section I, Toxicology Branch (7509C)
EPA Section Head: Roger L. Gardner
Review Section I, Toxicology Branch (7509C)

John E. Whalan Date: 8-14-96

Roger Gardner Date: 8/18/96

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization (Buehler Method) – Guinea Pigs (81-6)
OPPTS 870.2600 [§81-6]

DP BARCODE: D225354
P.C. CODE: 088002

SUBMISSION CODE: S504072
TOX. CHEM. NO: 357

TEST MATERIAL (purity): Zinc Omadine® 48% Dispersion (48% a.i.; Lot No. 5RC-088-024ZP)

SYNONYMS: Zinc pyrithione, zinc pyridinethione, bis(2-pyridylthio)zinc 1,1'-dioxide, bis-(1-hydroxy-2-(1H)-pyridinethionato-O,S)zinc, De-Squaman, Vancide ZP

CITATION: Theresa Newcomb. **Delayed Contact Dermal Sensitization Test (Buehler Method).** MB Research Laboratories, Inc., Spinnerstown, Pennsylvania. Study No. MB 96-4868.06. February 28, 1996. **MRID No. 43950201.** Unpublished.

SPONSOR: Olin Corporation, 120 Long Ridge Road, Stamford, CT 06904

EXECUTIVE SUMMARY: Following the Buehler Method, ten healthy male Hartley Albino guinea pigs were given 0.4 ml induction doses of undiluted Zinc Omadine 48% Dispersion once weekly for three weeks. Another group of 5 guinea pigs were naive controls. All animals were challenged with 0.4 ml doses of undiluted Zinc Omadine 48% Dispersion.

There was no evidence of dermal sensitization or irritation in any guinea pigs challenged with Zinc Omadine 48% Dispersion. There were also no compound-related clinical signs of body weight effects. The positive controls were sensitized when induced and challenged with DNCB.

This study is classified as **Acceptable**, and satisfies data requirement 81-6 for a Dermal Sensitization study in guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

MATERIALS AND METHODS: Fifteen healthy male Hartley Albino guinea pigs (283-337 g) were individually housed in suspended cages. Bedding was changed three-times weekly. Food and water were available *ad libitum*. Twenty-four hours prior to each dosing, the dorsal trunk skin was clipped free of hair to provide 5 cm x 10 cm dosing sites. Animals with irregularities or irritation, or any evidence of toxicity were eliminated. The study design was as follows:

	Induction		Challenge		
	Dose	**% Conc.**	**Dose**	**% Conc.**	**Animals**
Test article (induced)	0.4 ml	100%	0.4 ml	100%	10
Naive control for induced group	N/A	N/A	0.4 ml	100%	5

The test article, Zinc Omadine 48% Dispersion, was applied undiluted (i.e. 100% concentration). A group of 10 guinea pigs, the induced group, received 0.4 g induction doses on the left dorsal flank proximal cervical area. The site was covered with a Hilltop Chamber with a cotton pad, which in turn was occluded with a 2-3 inch wide strip of rubber dental dam wrapped with non-irritating tape.

After 6 hours of exposure, the dosing sites were washed with distilled water and towel-dried. Induction dose were administered once weekly over 3 consecutive weeks. Skin irritation scores were recorded 24 and 48 hours after each induction dose. The remaining 5 guinea pigs served as a naive control group, and received no induction doses. Positive control data were appended to the study report (MB Research Laboratories Study No. MB 95-4766.06; February 21, 1996). In a similar protocol, guinea pigs were induced with 0.2% DNCB and challenged with 0.1% DNCB.

Fourteen days after the last induction dosing, the induced and naive control guinea pigs received 0.4 g challenge doses by the same procedure as the induction doses, but on an untreated patch of skin. Skin irritation scores were recorded 24, 48, and 72 hours after the challenge dose. A score of 1 or greater at challenge in 20% or more of the animals was considered to be a sensitizing response. The guinea pigs were observed daily for clinical signs and mortality. Body weights were recorded pretest, 24 hours after the last induction dose, and 24 hours after the challenge dose.

RESULTS: No dermal irritation was observed in any animals during the induction or challenge phases. Weight gain in the induced guinea pigs lagged somewhat behind the naive controls, but not enough to be considered a toxic effect. Other than diarrhea in one animal, no clinical signs were observed. There was no evidence of dermal sensitization with Zinc Omadine 48% Dispersion. The positive controls induced and challenged with DNCB were sensitized.